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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,387	12/08/2003	Francis J. Giles	PHARMA-139	8138

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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,387	GILES ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,9,10,14,15,17-22,25-32,39-45 and 52-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,9,10,14,15,17-22,25-32,39-45 and 52-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 7, 9-10, 14-15, 17-22, 25-32, 39-45, and 52-64 are presented for examination

Applicants' amendment filed 11/13/2007 has been received and entered into the application. Accordingly, claims 63-64 have been added.

Applicants' arguments, filed 11/13/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Response to Arguments

Applicant's arguments filed 11/13/2007 have been fully considered but they are not persuasive.

Applicants argue that they have demonstrated synergistic results for the treatment of leukemia with the combination of (-)-L-OddC and STI-571 (page 9 of Response). Applicants assert that there is no suggestion that combining (-)-L-OddC and STI-571 will exhibit synergistic results. While it is true that one skilled in the art may not expect STI-571 to exhibit synergy with every anti-leukemic agent, the prior art demonstrates that STI-571 combined with four different anti-leukemic agent exhibited synergy. Accordingly, one skilled in the art would have been imbued with at least a reasonable expectation that STI-571 would be synergistic when combined with (-)-L-OddC. Given the state of the prior art, the skilled artisan would have been highly motivated to combine (-)-L-OddC with STI-571 to treat leukemia and would have reasonably

expected the combination to be synergistic given the fact that STI-571 combined with other anti-leukemic drugs having different structures and mechanisms of action demonstrated therapeutic synergy.

The rejection is maintained for the reasons of record and reiterated below.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1, 7, 9-10, 14-15, 17-22, 25-32, 39-45 and 52-64 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Chu *et al.*** (WO 96/07413), **Giles *et al.*** (JCO, 2001) and **Druker *et al.*** (N. Engl. J. Med., 2001, vol. 344, pages 1038-1042) in view of **Fang *et al.*** (Blood, 2000, vol. 96, pages 2246-2253) and **Topaly *et al.*** (Leukemia, 2001) (all prior art of record).

The instant claims are drawn to compositions comprising L-(-)-OddC (troxacitabine) and imatinib mesylate (STI-571) and methods of treating leukemia with said compositions.

Troxacitabine is well known in the art as a treatment for leukemia and is preferably used as its (-) enantiomer. For example, Chu *et al.* disclose the use of (-)-(*2S,4S*)-L-(2-hydroxymethyl-1,3-dioxolan-4-yl)cytosine (also referred to as (-)-OddC, L-OddC, or (-)-L-OddC) in the treatment of cancer (page 5, lines 17-27; page 47, Claim 12). The compound is administered as its substantially (-) enantiomer (*i.e.* free of the (+) enantiomer) (page 6, lines 6-11). Chu *et al.* define "enantiomerically enriched" to refer to a nucleoside composition that includes at least approximately 95%, and preferably approximately 97%, 98%, 99%, or 100% of a single enantiomer of that nucleoside. In a preferred embodiment, (-)-L-OddC or its derivative or salt is provided in a nucleoside composition that consists essentially of one enantiomer, *i.e.*, as the indicated enantiomer (the L-enantiomer) and substantially in the absence of its corresponding D-enantiomer (*i.e.*, in enantiomerically enriched, including enantiomerically pure form) (page 11, lines 6-18). Leukemia is recited as one type of cancer (-)-L-OddC can be used to treat (page 6, lines 22-28). It is further disclosed that (-)-L-OddC can be administered in combination with other anticancer agents, including interferons, interleukins and cytarabine (page 7, line 21 to page 8, line 20). Figure 3 shows the results of treatment of P388 (an experimental lymphocytic leukemia cell line) leukemic mice with (-)-L-OddC. Further, the *in vitro* activity of (-)-L-OddC was demonstrated against several different leukemia cell lines (Table 2, page 35).[1] These tested leukemia cell lines correspond to an acute lymphoblastic cell line (CCRF-CEM), an acute promyelocytic leukemia cell line (HL-60), a chronic myelogenous leukemia (CML) cell line (K-562) and an acute lymphoblastic leukemia cell line (MOLT-4).

[1] It is noted that the leukemia cell lines in Table 2 are not properly identified. It is believed that RL-60(TB) is HL-60; BSOLT-4 is MOLT-4; and RPMI-2.26 is RPMI-82.26.

Giles *et al.* is provided to show that the instantly claimed doses of (-)-L-OddC for the treatment of leukemia were known in the art. (-)-L-OddC (troxacitabine) is disclosed as being effective in the treatment of refractory or relapsed acute myeloid leukemia (AML) or lyphocytic (ALL) leukemia, myelodysplastic syndromes (MDS) or chronic myelogenous leukemia in blastic phase (CML-BP) (see especially Abstract). Troxacitabine was administered to patients in doses of 0.72 to 10 mg/m^2/day (page 765, Table 3). The MTD was determined to be 8 mg/m^2/day (Abstract).

Druker *et al.* is provided to show that the instantly claimed doses of imatinib mesylate (STI-571) for the treatment of leukemia were known in the art. STI-571 is a specific inhibitor of the Bcr-Abl tyrosine kinase and has been used to treat CML in blast crisis as well as ALL with the Philadelphia chromosome (*i.e.* ALL expressing Bcr-Abl) (see especially Abstract). Bcr-Abl is present in virtually all cases of CML and in 20% of cases of ALL. STI-571 was given orally at daily doses ranging from 300 to 1000 mg (Abstract; page 1040, Tables 4 & 5).[2]

Neither Chu *et al.*, Giles *et al.* nor Druker *et al.* disclose the specific combination of troxacitabine and imatinib mesylate, although Chu *et al.* does suggest that (-)-L-OddC can be combined with other chemotherapeutic agents (page 7, line 21 to page 8, line 20). Further, as Applicants acknowledge at pages 2-3 of the instant specification, combinations of two or more drugs are routinely administered as treatment for leukemia (*e.g.*, page 2, lines 4-15). In fact, as acknowledged by Applicants, STI-571 has been previously combined with other chemotherapeutics in the treatment of leukemia (page 3, lines 4-9).

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[2] The average male has a body surface area of 1.9 m^2, the average female, 1.6 m^2. Thus, the doses administered correspond to 0.16 g/m^2 to 0.53 g/m^2/d (males) and 0.19 g/m^2 to 0.63 g/m^2/d (females).

Fang *et al.* and Topaly *et al.* provide further motivation to combine STI-571 with other chemotherapeutic drugs wherein they disclose that combined therapies comprising STI-571 and other antileukemic drugs are synergistic when used to treat Bcr-Abl-positive human leukemia. For example, Fang *et al.* disclose that STI-571 induces hemoglobin levels and apoptosis of K562 and HL-60/Bcr-Abl leukemia cells (page 2249, right column). Co-treatment with STI-571 significantly increased the percentage of apoptotic cells following exposure to Ara-C or doxorubicin (Table 2). This effect was not observed in HL-60/neo cells, which do not express Bcr-Abl and are highly sensitive to apoptosis induced by Ara-C and doxorubicin (page 2251, left column). As conventional chemotherapy with Ara-C, doxorubicin and etoposide does not have major clinical efficacy against Bcr-Abl-positive acute leukemia or the blast crisis of CML, the data presented suggest that the effects of STI571 on these leukemias "may sensitize Bcr-Abl-positive human leukemic cells to apoptosis induced by antileukemic drugs" (page 2252, right column, last paragraph).

Further evidence of such synergism is found in Topaly *et al.* wherein STI-571 is demonstrated to have a synergistic effect when administered with other chemotherapeutic drugs on Bcr-Abl-positive CML cells (Abstract; Figure 2). The data provided therein implies that:

> "STI571 exhibits strong synergism with apoptosis-inducing cytarabine, mafosfamide and etoposide at higher levels of growth inhibition, which may originate from increasing inhibition of the BCR-ABL tyrosine kinase with subsequent induction of apoptotic pathways by these chemotherapeutic drugs" (page 346, right column).

Thus, the reference provides one skilled in the art with the motivation and reasonable expectation of success in treating Bcr-Abl-positive CML with a combination therapy of STI-571 and other chemotherapeutic agents.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

In the instant case, the prior art is replete with examples of chemotherapeutic agents being combined to treat cancer, including leukemia. In fact, combination chemotherapy has become commonplace in the treatment of cancer. Applicants acknowledge that the instantly claimed compounds have been previously used to treat leukemia and further acknowledge that STI-571 has been combined with other chemotherapeutic agents for the treatment of leukemia. The prior art also discloses methods of administration and doses of the instantly claimed compounds that can be used in the treatment of leukemia.

The prior art differs from the instant claims in that it does not explicitly teach the specific combination of chemotherapeutic agents instantly claimed. However, one of ordinary skill in the art (in this case, an M.D. with several years of experience) would have been highly motivated to combine two known antileukemic agents for the treatment of leukemia. As noted *supra*, such combinations are well known, in fact routine, in the art.

Accordingly, the instantly claimed formulations and methods of treating leukemia with a combination of (-)-L-OddC and imatinib mesylate would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The prior art discloses that both of these agents can be used to treat leukemia in the doses instantly claimed and further demonstrates that STI-571 has a synergistic effect when combined with other chemotherapeutic agents in the treatment of CML. As such, the skilled artisan has been provided with the explicit teaching that STI-571 can be combined with other chemotherapeutics and would be imbued with more than a reason expectation that such a combination would be effective (and likely synergistic) in the treatment of CML or other leukemias wherein Bcr-Abl is expressed (*e.g.* ALL). Further, in the absence of a showing of the criticality of the instantly claimed ratios of (-)-L-OddC to STI-571, such ratios would have been obvious to one of ordinary skill in the art and readily determined through routine optimization.

The motivation to combine the above references is explicitly found in Fang and Topaly as stated above. Moreover, (-)-L-OddC and STI-571 (*i.e.* imatinib mesylate) are individually known in the art as agents for treating leukemia, whose efficacy when administered alone is well established for the treatment of different leukemia types. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

It is not inventive to take two well-known antileukemia agents and combine them for the treatment of the same leukemias for which they are individually known in the art to be effective

in treating. As evidenced by the prior art and Applicants' admissions in the specification, such combination chemotherapy is routine in the art of treating cancer. Accordingly, to establish obviousness in such fact situations it is not necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed *supra*). The natural presumption that two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption.

Accordingly, the claims are deemed properly rejected as being an obvious modification of the prior art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

January 10, 2008

Ardin H. Marschel 1/12/08
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER